<u>Remarks</u>

Claims 1-4, 6, 11, 12 and 14-25 continue to be in the case.

There are objections to claims 1, 21 and 23 because of informalities and rejections of claim 23 and 24 under 35 U.S.C. 112, second paragraph, at pages 2-4 of the Detailed Action. Amendments are made herewith to overcome objections and rejections. Reconsideration is requested. Entry of the amendments is requested because the errors complained of are obvious and the corrections in response are obvious and because the amendments do not necessitate a further search.

Starting at page 4 of the Detailed Action, claims 1-4, 6-11, 12 and 14-25 are rejected under 35 U.S.C. 112, first paragraph, as being enabled only if (a)-(j) at page 4-6 of the Detailed Action were included in claim 1. Reconsideration is requested.

It is submitted that the inclusion of (a) – (j) would unfairly and unreasonably limit claim 1.

It is submitted that claim 1 is enabled without (a) – (j) because of the following.

The Examiner asserts that the specification does not teach the reliable classification of subjects as having or not having a tumor based upon the expression of at least two genes selected from manganese superoxide dismutase (MNSOD) genes, thioredoxine reductase 1 (TXNRD1) genes, and glutathione peroxidase 1 (GPX1) genes (see pages 29 and 30 of the office action). This assertion is respectfully traversed for the following reasons.

The specification teaches that based upon the expression of at least one gene selected from MNSOD genes, TXNRD1 genes and GPX1 genes, the sensitivity of correctly classifying a tumor patient as a subject having a tumor is 87, 67 and 62 %, respectively (see data from a working example at pages 46 and 47 of the instant specification). Note that almost 100 patients with various tumor types were included in this study.

It follows logically that the sensitivity will be even higher if the expression of at least two genes is determined. This is also corroborated by the fact that the determination of all three genes has a sensitivity of 93 %.

We submit that the working examples clearly corroborate that the method of the present invention enables the diagnosis of a tumor.

The Examiner further asserts that the specification does not teach the classification of subjects as at risk or not at risk to develop a metastasis or recurrence

(see page 30 of the office action). The data described in Professor Giesing's declaration are not found commensurate in scope with the claimed invention. It is said that the data include elements not disclosed in the originally filed specification such as the selection of individuals for diagnosis of prostate cancer based upon a serum PSA level between 4 to 10 ng/ml, and the particular gene combinations to predict the presence of distant metastasis or local metastasis, for example. That assertion, too, is respectfully traversed.

Firstly, the reason for selecting individuals having a serum PSA level between 4 to 10 ng/ml is the following. The detection rate of prostate cancer is believed to increase with increase in serum PSA. A threshold value of serum PSA at 4 ng/ml is often used for prostate biopsy. As the 4 to 10 ng/ml level is associated with a relatively low positive predictive value, the majority of biopsies remain without tumor diagnosis in patients having a serum PSA level between 4 to 10 ng/ml. Many of the tumors may thus be missed.

Because of these shortcomings and in order to demonstrate that the method of the present invention is superior to the tumor diagnosis based on serum PSA level, the patient group having a serum PSA level in the grey zone between 4 to 10 ng/ml was selected. However, this selection is not en element of the method of the present invention (and therefore said selection is not required to enable the method of the invention).

Secondly, the data in Professor Giesing's declaration show that the method of the

present invention even allows differentiating local from distant relapse thereby estimating the risk to develop a metastasis or recurrence. Whilst distant relapse was predicted with GPX1 and SOD2 (=MNSOD), local relapse was predicted with GPX1, SOD2 and TXNRD1.

Thirdly, we note that there is no claim specifically directed to differentiating local from distant relapse.

Fourthly, the instant specification teaches the combination of an MNSOD gene with a GPX1 gene as well as the combination of an MNSOD gene, GPX1 gene and TXNRD1 gene (page 5, lines 2–5 and lines 9–12).

Fifthly, the person of average skill in the art will be in a position to select particular gene combinations for addressing particular questions of diagnostic relevance.

Sixthly, the working examples described in the instant specification show that there was a clear correlation between the measured elevated expression of the MNSOD, TXNRD1 and GPX1 genes and the recurrences in the group of tumor patients tested. It is further stated that at least 2, and in particular all 3, parameters correlate better with the clinical course of a cancer than one parameter alone (see pages 51 to 53 under item 5 of the instant specification).

We therefore submit that the specification enables estimating the risk to develop

a metastasis or a recurrence.

The Examiner asserts that applicant has explicitly defined the term "manganese superoxide dismutase" to encompass both MNSOD and CuZnSOD (see pages 28 and 29 of the office action). We disagree.

The Examiner acknowledges that one skilled in the art would distinguish between MNSOD and CuZnSOD. How can the term "MNSOD" then be understood to encompass both MNSOD and CuZnSOD? The circumstance that the specification defines the term "MNSOD" to mean enzymes which catalyze a certain reaction does not mean that the term "MNSOD" encompasses any enzyme that catalyzes said reaction. By analogy, if the term "apple" is defined to mean fruits that have a red color, this does not mean that the term "apple" encompasses red berries.

The Examiner maintains that the specification fails to be enabling for determining any MNSOD gene, any TXNRD1 gene, or any GPX1 gene as there are different isoforms of MNSOD, TXNRD1 and GPX1 (page 29 of the office action). However, the Examiner fails to provide reasoning or evidence that one skilled in the art could not practice the invention without undue experimentation. In contrast, the working examples of the present application show that a large variety of disseminated cancer cells (i.e. breast, colon, prostate, ovary, lung, bladder, liver, thyroid and other cancer cells, see Example 2 on page 45–47) express the genes at stake in a manner which enables detection of said disseminated cancer cells with the method of the present invention. It the Examiner were correct in that cells from different tissues are expected

to express different isoforms of said genes, the working examples would show that it does not matter which isoform of the gene is expressed. Note that the primers and probes used in the working examples will amplify a number of transcript variants (see Professor Giesing's declaration on page 5).

The Examiner asserts that erythrocytes are a component of blood, and the claims encompass the use of these cells in the method (page 27 of the office action). That assertion, too, is respectfully traversed because erythrocytes do not contain genes and therefore it would not make sense to determine the expression of the genes at stake in erythrocytes.

The Examiner further contends that while comparisons other than the ones disclosed in the present specification may be used, further experimentation would be required to determine which comparisons provide a valid indication of the presence of disseminated cancer cells, the diagnosis of a tumor, and the risk to develop a metastasis or recurrence (see the office action on page 26).

We submit that this type of experimentation is routine in the art. It does not require inventive effort and would not be undue.

In principle, it is even not required to use any comparator cells at all.

The present invention is based on the finding that the migration of cancer cells away from the primary tumor and entry into the systemic vasculature is connected with the development of specific gene expression traits. More specifically, the invention is

based on the finding that such disseminated cancer cells overexpress genes involved in antioxidative protection. The inventors believe that said antioxidant overexpression in disseminated cancer cells can be described as a survival and defense mechanism required in an atypical environment. It is therefore the fundamental principle of the method of the present invention to determine whether the cells in a fraction obtained from the body fluid with enrichment of cancer cells overexpress the genes at stake. This does not necessarily require the use of comparative cells and determining the expression of the genes at stake in said comparative cells. If the working examples described in the specification and Professor Giesing's declaration use such comparative cells (MNCs), this is to address specific questions of clinical relevance and therefore the use of comparative cells is an optional measure which may be of advantage in certain situations.

One has to distinguish between the level of expression of a gene in a given cell and the ratio between the expression level of a gene in a first cell and the expression level of the same gene in a second cell.

For practical reasons, the absolute expression level is usually expressed as normalized cell equivalents (CEQ). To this end, the expression of a so-called housekeeping gene (e.g. GAPDH) is determined and the expression value obtained for the gene at stake is divided by the value obtained for the housekeeping gene so that the value obtained for the expression of the gene at stake does no longer depend on the number of cells in the sample subjected to measurement. Such a normalization is standard and well-known to the person skilled in the art.

It is also clear that the nature of the comparative cell does not affect the expression value determined on the cancer cell fraction (CEQ value). Only the ratio between the expression value of the cancer cells and the comparative cells may change depending on the kind of comparative cell used. Such ratios are referred to as relative specific expression (RSE) values and have to be distinguished from CEQ values.

Whether a certain CEQ value indicates the presence of a tumor or a risk to develop a metastasis or a recurrence is a matter of statistics. That is to say, the method needs to be validated on a number of patients in clinical settings, as reflected by the data presented in Professor Giesing's declaration. However, such a validation is not required for enabling the person skilled in the art to carry out the method. Moreover, we note that FDA approval is not required for a patent specification to be enabling. For instance, a dose finding study is not required for enabling a claim directed to a method of treating a disease by administering a drug.

In the present case, the Examiner appears to require final predictive and prognostic data for each tumor entity under any thinkable clinical circumstance and using each possible comparative cell. The Examiner may not be aware that the generation of such data may require years if not decades and enormous financial investment. It is safe to say that requiring applicants to provide such data to establish enablement is unreasonable.

We also note that the data on prostate cancer as presented in Professor

Giesing's declaration exceeds by far the data that are usually seen in patent applications. In fact, the data submitted may reach FDA's approval level. Just have a look at the Kaplan-Maier Diagram in Professor Giesing's declaration depicting the probability of relapse-free survival over the time. The time axis comprises more than 12 years!

The Examiner further asserts the one would not have reasonably expected to extrapolate the results provided in the present specification to the use of any body fluid.

The claims are drawn to a method for investigating blood or bone marrow for disseminated cancer cells. The working examples describe investigations on blood.

Given the dynamics of disseminated cancer cells in patient's tumor life, the compartment which is nearest to blood is bone marrow.

Although bone marrow sampling is invasive and therefore not readily available at any time point, the body of literature on the use of bone marrow samples in cancer diagnostics is of considerable size. As an example, we would like to focus on breast cancer. A review article has been published by the group of K. Pantel (Wölfe U, Müller V, and Pantel K, Disseminated Tumor Cells in Breast Cancer: Detection, Characterization and Clinical Relevance. Future Oncology, 2006: 2(4), 553–561). The full length paper is attached in PDF format. The reference list of this paper illustrates the history of tumor cell findings in bone marrow, originating from several decades ago.

We therefore submit that the method of the present invention can reasonably be expected to be applicable on bone marrow, also.

It is submitted that the claims as presently constituted provide reasonable scope for commercialization while the limits proposed in the office action do not and that such scope would be considered as reasonably enabled based on the above positions. The invention is obviously a good one and would save lives if not unreasonably and unfairly limited so that obtaining capital is not possible.

Respectfully submitted,

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B&T Docket No. GIES3002

Date: April 13, 2009